Relate

☐ **1:** Growth Factors 2001;18(4):251-9

GDF-8 propeptide binds to GDF-8 and antagonizes biological a inhibiting GDF-8 receptor binding.

Thies RS, Chen T, Davies MV, Tomkinson KN, Pearson AA, Shakey Q NM.

Genetics Institute, Inc., Cambridge, MA 02140, USA. sthies@genetics.com

GDF-8 is a new member of the TGF-beta superfamily which appears to be a regulator of skeletal muscle mass. Factors which regulate the biological acti 8 have not yet been identified. However, the biological activities of TGF-be superfamily members, TGF-beta1, -beta2 and -beta3, can be inhibited by nc association with TGF-beta1, -beta2 and beta3 propeptides cleaved from the termini of the TGF-beta precursor proteins. In contrast, the propeptides of o beta superfamily members do not appear to be inhibitory. In this investigati demonstrate that purified recombinant GDF-8 propeptide associates with pu recombinant GDF-8 to form a noncovalent complex, as evidenced by size e chromatography and chemical crosslinking analysis. Furthermore, we show propeptide inhibits the biological activity of GDF-8 assayed on A204 rhabdomyosarcoma cells transfected with a (CAGA)12 reporter construct. I demonstrate that GDF-8 propeptide inhibits specific GDF-8 binding to L6 r cells. Collectively, these data identify the GDF-8 propeptide as an inhibitor biological activity.

PMID: 11519824 [PubMed - in process]

☐ **2:** Proc Natl Acad Sci U S A 2001 Apr 24;98 (9):5104-9 Related Articles, Nucleotide, OMIM

Mutation in bone morphogenetic protein receptor-IB is associa increased ovulation rate in Booroola Merino ewes.

Mulsant P, Lecerf F, Fabre S, Schibler L, Monget P, Lanneluc I, Pissel J, Monniaux D, Callebaut I, Cribiu E, Thimonier J, Teyssier J, Bodin L Chitour N, Elsen JM.

Institut National de la Recherche Agronomique, Laboratoire de Genetique C BP, 27, 31326 Castanet-Tolosan, France. mulsant@toulouse.inra.fr

Ewes from the Booroola strain of Australian Merino sheep are characterize ovulation rate and litter size. This phenotype is due to the action of the FecI a major gene named FecB, as determined by statistical analysis of phenotyp genetic analysis of 31 informative half-sib families from heterozygous sires that the FecB locus is situated in the region of ovine chromosome 6 corresp human chromosome 4q22-23 that contains the bone morphogenetic protein (BMPR-IB) gene encoding a member of the transforming growth factor-bet receptor family. A nonconservative substitution (Q249R) in the BMPR-IB c sequence was found to be associated fully with the hyperprolificacy phenot Booroola ewes. In vitro, ovarian granulosa cells from FecB(B)/FecB(B) ew responsive than granulosa cells from FecB(+)/FecB(+) ewes to the inhibitor steroidogenesis of GDF-5 and BMP-4, natural ligands of BMPR-IB. It is su in FecB(B)/FecB(B) ewes, BMPR-IB would be inactivated partially, leadin advanced differentiation of granulosa cells and an advanced maturation of c follicles.

PMID: 11320249 [PubMed - indexed for MEDLINE]

☐ **3:** J Neural Transm Suppl 2000;(60):273-6 Relate

GDF-15/MIC-1 a novel member of the TGF-beta superfamily.

Strelau J, Bottner M, Lingor P, Suter-Crazzolara C, Galter D, Jaszai J Schober A, Krieglstein K, Unsicker K.

Neuroanatomy and Center for Neuroscience, University of Heidelberg, Fed of Germany.

We have cloned, expressed, and raised antibodies against a novel member c beta superfamily, growth/differentiation factor-15 (GDF-15). The predicted identical to macrophage inhibitory cytokine-1 (MIC-1), which was discover simultaneously. GDF-15 is a more distant member of the TGF-beta superfa not belong to one of the known TGF-beta subfamilies. In the CNS, GDF-15 mRNA is abundantly expressed by the choroid plexus. In addition we have evidence that GDF-15/MIC-1 is a potent trophic factor for selected classes vitro and in vivo. Thus, GDF-15 is a novel neurotrophic factor with prospec treatment of disorders of the CNS.

Publication Types:

- Review
- Review, tutorial

PMID: 11205146 [PubMed - indexed for MEDLINE]

Relate

4: Ann N Y Acad Sci 2000;919:86-96

Mechanisms of cell transformation in the Syrian hamster embr cell transformation system.

Isfort RJ.

Research Division, Procter & Gamble Pharmaceuticals, Cincinnati, Ohio 4: USA. isfortrj@pg.com

The Syrian hamster embryo (SHE) cell transformation system has been use investigational studies of basic mechanisms of neoplastic transformation, a determining the carcinogenic potential of chemical, physical, and biological Many of these investigations utilize an intermediate step in the SHE cell ne transformation process, known as morphological transformation, as an indi cells have acquired an increased potential to progress to malignancy. While the morphologically transformed phenotype is not completely understood, i to result from a block in the cellular differentiation of stem cells present wi cell population. In terms of determination of the transforming potential of biological/chemical/physical agents, more than 500 agents have been tested cell transformation assay with an 80-90% correlation between MT and carc potential. As such, the SHE cell transformation assay has utility as a test to short-term information on the carcinogenic potential of chemicals. One clas current interest with regard to SHE cell transformation assay utilization con growth and differentiation factors (GDFs). Analysis of the SHE cell transfo potential of the GDFs, epidermal growth factor (EGF), fibroblast growth fa 4), platelet-derived growth factor AA (PDGF AA), PDGF AB, PDGF BB, a antimitogenic GDF, transforming growth factor beta one (TGF-beta1), was All GDFs, with the exception of TGF-beta1, induced SHE cell transformati an interesting difference between the GDFs was observed--PDGF A/B and but not PDGF A/A, EGF, or FGF-4, induced transformation after both a tra exposure and a continuous 7-day exposure, while continuous 7-day exposu required for transformation by PDGF A/A, EGF, and FGF-4. Interestingly, 1-day and continuous 7-day TGF-beta1 exposure resulted in suppression of transformation induced by a variety of transforming agents including growt Ames assay-positive carcinogens, Ames assay-negative carcinogens, and sp transformation. Interestingly TGF-beta1 was not able to suppress transform tumor promoter, TPA. Together, these data demonstrate the utility of the Sy embryo cell transformation system for analyzing the transforming potential for characterizing differences in transforming mechanisms between differer

PMID: 11083101 [PubMed - indexed for MEDLINE]

☐ 5: Expert Opin Investig Drugs 2000 Apr;9(4):747-64 Related Articles

Apoptosis modulators in the therapy of neurodegenerative dise

Deigner HP, Haberkorn U, Kinscherf R.

Anatomy and Cell Biology III University of Heidelberg, Germany.

Apoptosis is a prerequisite to model the developing nervous system. Howev increased rate of cell death in the adult nervous system underlies neurodege disease and is a hallmark of multiple sclerosis (MS) Alzheimer's- (AD), Par or Huntington's disease (HD). Cell surface receptors (e.g., CD95/APO-1/Fa receptor) and their ligands (CD95-L; TNF) as well as evolutionarily conser mechanisms involving proteases, mitochondrial factors (e.g. , Bcl-2-related reactive oxygen species, mitochondrial membrane potential, opening of the transition pore) or p53 participate in the modulation and execution of cell d Effectors comprise oxidative stress, inflammatory processes, calcium toxici survival factor deficiency. Therapeutic agents are being developed to interfe events, thus conferring the potential to be neuroprotective. In this context, d anti-oxidative properties, e.g., flupirtine, N-acetylcysteine, idebenone, mela also novel dopamine agonists (ropinirole and pramipexole) have been show neuronal cells from apoptosis and thus have been suggested for treating neurodegenerative disorders like AD or PD. Other agents like non-steroidal inflammatory drugs (NSAIDs) partly inhibit cyclooxygenase (COX) expres as having a positive influence on the clinical expression of AD. Distinct cyt growth factors and related drug candidates, e.g., nerve growth factor (NGF) of the transforming growth factor-beta (TGF-beta) superfamily, like growtl differentiation factor 5 (GDF-5), are shown to protect tyrosine hydroxylase dopaminergic neurones from apoptosis. Furthermore, peptidergic cerebroly found to support the survival of neurones in vitro and in vivo. Treatment wi inhibitors are suggested as potential targets to prevent DNA fragmentation i dopaminergic neurones of PD patients. Finally, CRIB (cellular replacement immunoisolatory biocapsule) is an auspicious gene therapeutical approach f NGF secretion, which has been shown to protect cholinergic neurones from when implanted in the brain. This review summarises and evaluates novel a anti-apoptotic concepts and pharmacological intervention including gene th approaches currently being proposed or utilised to treat neurodegenerative c

Publication Types:

- Review
- Review, academic

PMID: 11060707 [PubMed - indexed for MEDLINE]

☐ 6: Bone 2000 Sep;27(3):343-9 Related Articles

Femoral morphology and cross-sectional geometry of adult my

deficient mice.

Hamrick MW, McPherron AC, Lovejoy CO, Hudson J.

Department of Anthropology & School of Biomedical Sciences, Kent State
Kent, OH 44242, USA. mhamrick@kent.edu

GDF-8, also known as myostatin, is a member of the transforming growth f
(TGF-beta) superfamily of secreted growth and differentiation factors that i
vertebrate skeletal muscle. Myostatin functions as a negative regulator of sk
growth and myostatin null mice show a doubling of muscle mass compared
mice. We examined femoral morphology of adult myostatin-deficient mice
effects of muscle fiber hypertrophy and hyperplasia on bone shape and cros
geometry. Femora of age- and weight-matched adult mice homozygous for
myostatin sequence were compared with those of wild-type controls (n = 8
Results show that, as was the case in previous studies, myostatin null mice
hindlimb muscle masses that are approximately double those of controls. M
deficient mice exhibit third trochanters that are significantly larger than tho
whereas the femoral midshafts of the control and experimental mice do not
significantly from one another in cortical area, bending moment of inertia, a
moment of inertia. Our findings indicate that the increased muscle mass of
deficient mice primarily affects sites of muscle insertion, but does not induc
cortical bone deposition in the diaphysis relative to controls. We therefore c
the expanded third trochanters of myostatin-deficient subjects result from te
Sharpey fiber expansion associated with muscle growth rather than cortical
deposition in response to increased levels of mechanical stress.

PMID: 10962344 [PubMed - indexed for MEDLINE]

☐ 7: Mech Dev 2000 Jul;95(1-2):279-82 Related Articles, Nucleotide, Protein

**Gdf16, a novel member of the growth/differentiation factor sul
the TGF-beta superfamily, is expressed in the hindbrain and e
placodes.**

Vokes SA, Krieg PA.

Department of Cell Biology and Anatomy, University of Arizona Health Sc
Center, P.O. Box 245044, Tucson, AZ 85724, USA.

We have isolated and characterized the developmental expression of Xenop
novel member of the growth/differentiation factor (gdf) gene family. The g
encodes a pre-proprotein of 413 amino acids and a mature peptide of 122 a
Gdf16 is most closely related to the zebrafish genes dynamo and radar, but
completely different expression pattern. Gene expression is detected at earl
(stage 25) in the first two epibranchial placodes and in a hindbrain-specific
development proceeds, the gene is expressed in all the epibranchial placode

hindbrain, and the diencephalon.

PMID: 10906478 [PubMed - indexed for MEDLINE]

☐ **8:** Vitr Mol Toxicol 1999;12(3):133-148 Relate

Analysis of the Transforming Potential of Growth and Differe Factors in Syrian Hamster Embryo Cells: Reversible and Irre Transformation.

Isfort RJ, Cody DB, Kerckaert GA, LeBoeuf RA.

Corporate Professional & Regulatory Services, The Procter & Gamble Com Valley Laboratories, Cincinnati, Ohio 45253-8707.

The mitogenic growth and differentiation factor (GDFs) oncostatin M (OM growth factor (EGF), fibroblast growth factor 4 (FGF-4), platelet-derived gr AA (PDGF AA), PDGF AB, and PDGF BB and the anti-mitogenic GDF, tr growth factor beta one (TGF-beta1), were tested in the 7-day continuous ex 24-h transient exposure Syrian hamster embryo (SHE) cell transformation a determine their reversible and irreversible transforming potential. OM was while EGF, FGF-4, and PDGF AA were positive for statistically significant morphological transformation (MT) in the 7-day exposure SHE cell transfo assay. PDGF AB and PDGF BB (but not EGF, FGF-4, and PDGF AA) wer statistically significant MT in the 24-h transient exposure SHE cell transfor assays. TGF-beta1 was not only negative for the induction of MT in the 7-d exposure SHE cell transformation assays, but suppressed the spontaneous b transformation response. Investigation of the transformation suppression po TGF-beta1 demonstrated that TGF-beta1 was able to irreversibly suppress t transformation potential of a variety of transforming agents including growt Ames assay positive carcinogens, and Ames assay negative carcinogens. PI PDGF BB were investigated to better understand the reversible and irrevers transformation response. Differences in the receptors activated, the proteins phosphorylated by the receptors, and immediate early gene expressed were SHE cells treated with either PDGF AA or PDGF BB. Importantly, SHE ce with TGF-beta1 and PDGF BB, two GDFs, which modulate SHE cell trans irreversibly, altered DNA methylation; PDGF AA did not demonstrate this Together these data demonstrate that the SHE cell transformation assay can evaluate the transformation potential and mechanism of activation of GDFs

PMID: 10894764 [PubMed - as supplied by publisher]

☐ **9:** Trends Endocrinol Metab 2000 Jul;11(5):193-8 Related Articles

Full Text ...on BioMedNet GO

The role of the oocyte in folliculogenesis.

Erickson GF, Shimasaki S.

Department of Reproductive Medicine, University of California, San Diego CA 92093-0674, USA. gerickson@ucsd.edu

Novel regulatory proteins have been identified within oocytes that are cruci in folliculogenesis. One of the most exciting oocyte signaling molecules is a member of the transforming growth factor beta (TGF-beta) superfamily, gro differentiation factor 9 (GDF-9). Loss-of-function studies have established obligatory for proper folliculogenesis and fertility in female mice. The curre are to understand how oocyte morphogens regulate folliculogenesis and hov actions and interactions are integrated into the overall processes of physiolo pathophysiology. Who would have thought that oocyte morphogens would for reproduction?

Publication Types:
- Review
- Review, tutorial

PMID: 10856922 [PubMed - indexed for MEDLINE]

☐ **10:** Growth Factors 2000;17(4):269-85 Relate

Induction of endochondral bone formation by recombinant hu transforming growth factor-beta2 in the baboon (Papio ursinu

Ripamonti U, Crooks J, Matsaba T, Tasker J.

Bone Research Laboratory, Medical Research Council/University of the Wi Medical School, Johannesburg, South Africa. 177RIPA@chiron.wits.ac.za

Members of the transforming growth factor-beta (TGF-beta) superfamily, tl morphogenetic and osteogenic proteins (BMPs/OPs) but not the TGF-beta p themselves, induce endochondral bone formation in vivo, when implanted i extraskeletal heterotopic sites of rodents. Here we show that recombinant hu beta2 (hTGF-beta2) induces endochondral bone formation 30 days after imp heterotopic intramuscular sites of the baboon (Papio ursinus) at doses of 1, microg per 100 mg of guanidinium-inactivated collagenous bone matrix as day 90 there was generation of large radiopaque and corticalized intramuscu Five and 25 microg hTGF-beta2 induced large ossicles in the rectus abdomi primate as evaluated by key parameters of bone formation, including genera area, mineralized bone and osteoid volumes, and tissue alkaline phosphatas day 30 and 90 after healing, hTGF-beta2 also induced bone formation wher the rectus abdominis in conjunction with a sintered porous hydroxyapatite a mRNA expression in tissues from heterotopic specimens showed OP-1 (BM BMP-3 transcripts in low abundance and with a linear dose-dependent incre collagenous matrix and hydroxyapatite samples. Type IV collagen mRNA e

marker of angiogenesis, was stronger in collagenous than hydroxyapatite sa
Growth and differentiation factor-10 (GDF-10) mRNA transcripts were exp
ossicles with a distinctly chondrogenic phase, but its expression was greate
generated in porous hydroxyapatites, in which bone formation is not via a c
phase, but is rather intramembranous, without expression of type II collage
the same animals, however, 10 and 100 microg of the recombinant morpho
by identical carriers (collagenous matrix and sintered hydroxyapatite) failed
calvarial defects. Thus in the primate, TGF-betas themselves are inducers o
endochondral bone formation, although the present data strongly indicate th
inductive activity of hTGF-beta2 is site and tissue specific, since a single ap
hTGF-beta2, or hTGF-beta1 in previously published experiments, did not in
calvarial defects, but did induce endochondral bone differentiation in heterc

PMID: 10801076 [PubMed - indexed for MEDLINE]

☐ **11:** Nat Genet 2000 Mar;24(3):262-5 Related Articles, OMIM

nature genetics

Regulation of left-right patterning in mice by growth/different factor-1.

Rankin CT, Bunton T, Lawler AM, Lee SJ.

Department of Molecular Biology and Genetics, Baltimore, Maryland, USA

The transforming growth factor-beta (TGF-beta) superfamily encompasses
of structurally related polypeptides that are capable of regulating cell growt
differentiation in a wide range of embryonic and adult tissues. Growth/diffe
factor-1 (Gdf-1, encoded by Gdf1) is a TGF-beta family member of unknov
that was originally isolated from an early mouse embryo cDNA library and
specifically in the nervous systemin late-stage embryos and adult mice. Her
that at early stages of mouse development, Gdf1 is expressed initially throug
embryo proper and then most prominently in the primitive node, ventral ne
intermediate and lateral plate mesoderm. To examine its biological functior
generated a mouse line carrying a targeted mutation in Gdf1. Gdf1-/- mice e
spectrum of defects related to left-right axis formation, including visceral si
right pulmonary isomerism and a range of cardiac anomalies. In most Gdf1-
the expression of Ebaf (formerly lefty-1) in the left side of the floor plate ar
(formerly lefty-2), nodal and Pitx2 in the left lateral plate mesoderm was ab
suggesting that Gdf1 acts upstream of these genes either directly or indirect
their expression. Our findings suggest that Gdf1 acts early in the pathway o
activation that leads to the establishment of left-right asymmetry.

PMID: 10700179 [PubMed - indexed for MEDLINE]

☐ **12:** J Reprod Fertil Suppl 1999;54:3-16 Relate

Control of early ovarian follicular development.

McNatty KP, Heath DA, Lundy T, Fidler AE, Quirke L, O'Connell A, Groome N, Tisdall DJ.

Wallaceville Animal Research Centre, Upper Hutt, New Zealand.

Early follicular growth refers to the development of an ovarian follicle from primordial to early antral phase. In sheep and cows these phases of growth c classified by the configuration of granulosal cells in the largest cross-sectio follicle as types 1 (primordial), 1a (transitory) 2 (primary), 3 and 4 (preantr (early antral). Follicles classified as type 1 may be highly variable within ea with respect to number of granulosal cells and diameter of oocyte. Much of in granulosal cell composition of type 1 follicles may occur at formation an account for the variability in granulosal cell composition throughout subseq growth. There appear to be important differences among species (for examp cattle) in the number and function of granulosal cells relative to the diamete oocyte during the initiation of follicular growth. There is evidence that mos the growth phases from types 1 to 5 are gonadotrophin-independent and tha develop in a hierarchical manner. In sheep, cows and pigs, numerous growt growth factor receptor and gonadotrophin receptor mRNAs and peptides (f kit, stem cell factor, GDF-9, beta B and beta A activin/inhibin subunit, alph subunit, follistatin, FGF-2, EGF, EGF-R, TGF beta 1,2 and 3 FSH-R and L expressed in a phase of growth (for example types 1-5)-specific and cell-sp However, the roles of many of these factors remain to be determined.

Publication Types:
- Review
- Review, tutorial

PMID: 10692841 [PubMed - indexed for MEDLINE]

☐ **13:** Mol Cell Endocrinol 2000 Jan 25;159(1-2):1-5 Related Articles

Oocyte-expressed TGF-beta superfamily members in female fe

Elvin JA, Yan C, Matzuk MM.

Department of Pathology, Baylor College of Medicine, Houston, TX 77030

Folliculogenesis is regulated by the interplay of extraovarian and intraovari and the importance of each type of regulation varies depending on the devel stage of the follicle. Preantral follicle development is regulated predominan produced locally within the ovary and within the follicle itself. The oocyte l shown to produce soluble factor(s), which regulate a number of processes i development, including cumulus expansion in the periovulatory period. Me TGFbeta superfamily are potent regulators of cell proliferation and differen

number of organ systems, and three members, growth differentiation factor bone morphogenetic protein 15 (BMP-15) and BMP-6 are expressed by the may mediate effects attributed to the oocyte. Based on knockout mouse mo does not play an essential role in ovarian function, but GDF-9 is absolutely preantral follicle development. GDF-9 also alters the periovulatory expressi granulosa cell genes and stimulates cumulus expansion. Although BMP-15 identically to GDF-9, its role in regulating ovarian function is still unknowr examines the similarities and differences in sequence, expression, and funct oocyte-expressed TGFbeta family members with respect to regulating follic

Publication Types:

- Review
- Review, tutorial

PMID: 10687846 [PubMed - indexed for MEDLINE]

☐ **14:** Blood Cells Mol Dis 1999 Oct-Dec;25(5-6):310-23 Related Articles

IDEAL

Lineage-restricted expression of bone morphogenetic protein g human hematopoietic cell lines.

Detmer K, Steele TA, Shoop MA, Dannawi H.

Division of Basic Medical Sciences, Mercer University School of Medicine 31207, USA. detmer.k@gain.mercer.edu

To explore the possibility that bone morphogenetic proteins (BMPs) are autocrine/paracrine regulators of hematopoietic differentiation and function a panel of human cell lines encompassing the hematopoietic lineages for ex members of this family of genes. Expression of BMP-2, BMP-4, BMP-6, B Growth and Differentiation Factor-1 (GDF-1), Placental Bone Morphogene (PLAB), and Transforming Growth Factor-beta3 (TGF-beta3) was detected more cell lines. BMP-2, BMP-4, BMP-7, and TGF-beta3 expression was al normal hematopoietic tissue. Expression of BMP-5 and BMP-8 was not see restricted patterns of expression were found for BMP-4 (T-lymphoid), BMI (lymphoid), PLAB (macrophage/monocyte), and GDF-1 (myeloid). Expres 2, GDF-1, and PLAB could be modulated by treatment with differentiating Marked variations in the levels of BMP-4, BMP-7, and PLAB expression w encountered, indicating that disorders in BMP signaling pathways may play development of hematopoietic neoplasia. Copyright 1999 Academic Press.

PMID: 10660478 [PubMed - indexed for MEDLINE]

☐ **15:** J Neurosci 2000 Dec 1;20(23):8597-603 Related Articles

Full text article at www.jneurosci.org

Growth/differentiation factor-15/macrophage inhibitory cytok novel trophic factor for midbrain dopaminergic neurons in viv

Strelau J, Sullivan A, Bottner M, Lingor P, Falkenstein E, Suter-Crazz Galter D, Jaszai J, Krieglstein K, Unsicker K.

Neuroanatomy and Interdisciplinary Center for Neurosciences, University o D-69120 Heidelberg, Germany.

Transforming growth factor-betas (TGF-betas) constitute an expanding fam multifunctional cytokines with prominent roles in development, cell prolife differentiation, and repair. We have cloned, expressed, and raised antibodie distant member of the TGF-betas, growth/differentiation factor-15 (GDF-1: identical to macrophage inhibitory cytokine-1 (MIC-1). GDF-15/MIC-1 mR protein are widely distributed in the developing and adult CNS and periphe systems, including choroid plexus and CSF. GDF-15/MIC-1 is a potent sur promoting and protective factor for cultured and iron-intoxicated dopamine (DAergic) neurons cultured from the embryonic rat midbrain floor. The tro GDF-15/MIC-1 was not accompanied by an increase in cell proliferation an maturation, suggesting that GDF-15/MIC-1 probably acts directly on neuro 15/MIC-1 also protects 6-hydroxydopamine (6-OHDA)-lesioned nigrostriat neurons in vivo. Unilateral injections of GDF-15/MIC-1 into the medial for just above the substantia nigra (SN) and into the left ventricle (20 microgra immediately before a 6-OHDA injection (8 microgram) prevented 6-OHDA rotational behavior and significantly reduced losses of DAergic neurons in t protection was evident for at least 1 month. Administration of 5 microgram 15/MIC-1 in the same paradigm also provided significant neuroprotection. 15/MIC-1 also promoted the serotonergic phenotype of cultured raphe neur not support survival of rat motoneurons. Thus, GDF-15/MIC-1 is a novel n factor with prominent effects on DAergic and serotonergic neurons. GDF-1 therefore have a potential for the treatment of Parkinson's disease and disor serotonergic system.

PMID: 11102463 [PubMed - indexed for MEDLINE]

☐ **16:** Mol Cell Endocrinol 1999 Oct 25;156(1-2):189-93 Related Articles, Nucleotide

Localization of growth differentiation factor-9 (GDF-9) mRNA protein in rat ovaries and cDNA cloning of rat GDF-9 and its r homolog GDF-9B.

Jaatinen R, Laitinen MP, Vuojolainen K, Aaltonen J, Louhio H, Heiki Lehtonen E, Ritvos O.

Department of Bacteriology and Immunology, Haartman Institute, Universi
Helsinki, Finland.

Although targeted gene disruption of GDF-9, an oocyte derived growth fact
an arrest of folliculogenesis and causes infertility in female mice, little is kr
expression of GDF-9 protein in the ovary. We show that GDF-9 protein is e
rat oocytes during folliculogenesis from the early primary follicle stage onw
most intensive immunostaining was seen in primary and preantral follicles.
analyses of the ontogeny of GDF-9 gene expression in postnatal rat ovaries
the GDF-9 transcript levels are clearly increased on the second postnatal da
concomitant with the appearance of primary follicles. Interestingly, Norther
situ hybridization analyses indicate a similar expression pattern for GDF-9I
ortholog of a mouse GDF-9 like factor for which we recently reported the p
acid sequence. The polypeptide sequences deduced from isolated ovarian cl
indicate that the rat GDF-9 prepropeptide is 440 amino acids (aa) in length
putative mature peptide is 135 aa whereas rat GDF-9B is 391 aa long and th
region is 125 aa. We conclude that (1) the GDF-9 protein is highly expresse
oocytes of primary follicles of rat ovaries suggesting that it plays a role mai
folliculogenesis and that (2) the full-length polypeptide sequence of GDF-9
that this novel TGF-beta family member is likely to be a secreted growth fa
regulate folliculogenesis at similar developmental stages as GDF-9.

PMID: 10612437 [PubMed - indexed for MEDLINE]

☐ **17:** Gene 1999 Sep 3;237(1):105-11 Related Articles, Nucleotide, OMIM, Protein

Characterization of the rat, mouse, and human genes of growth/differentiation factor-15/macrophage inhibiting cytoki 15/MIC-1).

Bottner M, Laaff M, Schechinger B, Rappold G, Unsicker K, Suter-Cr

Department of Neuroanatomy, University of Heidelberg, Germany.
un691mb@genius.embnet.dkfz-heidelberg.de

We have isolated the rat, mouse and human genes of a distant member of th
superfamily, growth/differentiation factor-15/macrophage inhibiting cytoki
15/MIC-1) by screening of genomic libraries. All three genes are composed
exons, and contain one single intron that interrupts the coding sequences at
positions within the prepro-domain of the corresponding proteins. The pred
contain the structural hallmarks of members of the TGF-beta superfamily, i
seven conserved carboxy-terminal cysteine residues that form the cystine kr
orthologous molecules show the lowest sequence conservation of all memb
TGF-beta superfamily. RT-PCR reveals an abundant expression of GDF-15
mRNA in numerous embryonic and adult organs and tissues. Promoter anal
promoter indicates the presence of multiple regulatory elements, including a
sequence as well as several SP1, AP-1 and AP-2 sites. Deletion analysis su
350 bp region upstream of the start of the open reading frame appears to be

important for regulation of transcription.

PMID: 10524241 [PubMed - indexed for MEDLINE]

☐ **18:** Genomics 1999 Aug 15;60(1):87-95 Related Articles, Nucleotide

Cloning, expression profile, and genomic organization of the m STAP/A170 gene.

Okazaki M, Ito S, Kawakita K, Takeshita S, Kawai S, Makishima F, O Kakinuma A.

Discovery Research Laboratories, Hoechst Marion Roussel Ltd., Kawagoe, Japan.

The preferential screening of cDNA libraries derived from the mouse osteol line MC3T3-E1 has yielded a cDNA clone encoding a 442-amino-acid prot designated STAP (signal transduction and adaptor protein), which contains motifs shared among transcription factors and adaptors such as a Zn-finger proline-rich domain, and a PEST sequence. The amino acid sequence homo also reveals that STAP is identical to a mouse oxidative stress protein, A17 90% homology with a human p62 protein that binds to the tyrosine kinase p domain. Northern blot analysis indicated a broad expression profile of STA various tissues and cell lines. In MC3T3-E1 cells, STAP mRNA was induc treatment with TGF-beta, but not with BMP-2 or GDF-5. Analysis of the m gene isolated from the genomic library revealed that the STAP gene spans a over 11 kb and comprises eight exons. The transcription start site was ident primer extension analysis to be located 35 bp upstream from the translation site. Sequencing analysis of the 5' flanking region of the STAP gene reveale consensus motifs/sequences for several DNA binding transcription factors. gene had a TATA box, but no CCAAT box. Potential Sp1, AP-1, NF-E2, M NF-kappaB binding sites were found in the 5' flanking region (1.4 kb) of th

PMID: 10458914 [PubMed - indexed for MEDLINE]

☐ **19:** Dev Biol 1999 Aug 1;212(1):68-79 Related Articles

Characterization of GDF-10 expression patterns and null mice

Zhao R, Lawler AM, Lee SJ.

Department of Molecular Biology and Genetics, Department of Gynecology Obstetrics, Johns Hopkins University School of Medicine, 725 North Wolfe

Baltimore, Maryland, 21205, USA.

Growth/differentiation factor-10 (GDF-10) is a TGF-beta family member hi to bone morphogenetic protein-3. In order to determine the biological funct 10, we carried out a detailed analysis of the expression pattern of GDF-10 a characterized GDF-10-null mice that we generated by gene targeting. Durin embryogenesis GDF-10 is expressed prominently in developing skeletal str in the craniofacial region and in the vertebral column. In adult animals, GD expressed at high levels in the brain, where GDF-10 is localized primarily t Purkinje cell layer of the cerebellum, and in the uterus, where the expressio GDF-10 are regulated both during the menstrual cycle and during pregnanc high levels of GDF-10 expression in these tissues, we found no obvious abr GDF-10-knockout mice with respect to the development of these tissues. Tl suggest either that GDF-10 plays no regulatory role in these tissues or that i redundant with that of other growth factor-like molecules. Copyright 1999 Press.

PMID: 10419686 [PubMed - indexed for MEDLINE]

☐ **20:** Exp Cell Res 1999 Aug 1;250(2):351-63 Related Articles

IDEAL

p38 mitogen-activated protein kinase functionally contributes chondrogenesis induced by growth/differentiation factor-5 in A cells.

Nakamura K, Shirai T, Morishita S, Uchida S, Saeki-Miura K, Makish

Discovery Research Laboratories, Hoechst Marion Roussel Ltd., 3-2, Mina chome, Kawagoe, Saitama, 350-1165, Japan.

Recent studies of intracellular signal transduction mechanisms for the trans growth factor-beta (TGF-beta) superfamily have focused on Smad proteins, paid little attention to mitogen-activated protein (MAP) kinase cascades. H demonstrate that growth/differentiation factor-5 (GDF-5), but neither bone morphogenetic protein-2 (BMP-2) nor TGF-beta1, fully promotes the early chondrogenic response by inducing cellular condensation followed by cartil formation in a mouse chondrogenic cell line, ATDC5. We investigated whi the three major types of MAP kinase plays a functional role in the promotio chondrogenesis induced by GDF-5. GDF-5 induced phosphorylation of p38 and extracellular signal-regulated kinase (ERK) but not that of c-Jun N-tern (JNK). The phosphorylation of p38 MAP kinase was also induced by BMP- beta1. An inhibitor of p38 and p38 beta MAP kinase, SB202190, showed c inhibition of cartilage nodule formation but failed to affect alkaline phosph activity induced by GDF-5. Expression of the type II collagen gene, a hallm chondrogenesis in vertebrates, was also induced by GDF-5 treatment and st suppressed by SB202190. On the other hand, although an inhibitor of MAP PD98059, inhibited the rapid phosphorylation of ERK by GDF-5, it inhibit

ALP activity nor cartilage nodule formation induced by GDF-5. These resul suggest that the p38 MAP kinase cascade is involved in GDF-5 signaling pa that a role of the p38 MAP kinase pathway is necessary over a longer perioc chondrogenesis in ATDC5 cells. Copyright 1999 Academic Press.

PMID: 10413589 [PubMed - indexed for MEDLINE]
